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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,171	01/03/2002	Robert Haley	UTSD:749US	7156

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,171	HALEY ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9-25* is/are pending in the application.

4a) Of the above claim(s) *2,22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,9-21,23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 1-5 and 9-25 are pending.

Applicant's traversal, the amendment to claims 1, 21, and 22-24, the cancellation of claims 6-8 and 30 filed on 2/23/06 is acknowledged and considered by the examiner.

Election/Restrictions

Claim 2 remains and claim 22 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/14/05.

Claim 22 as amended now reads on a nonelected invention (PON1 type Q).

Upon further consideration of the prior art not teaching and enabling the claimed method, the non-elected species in claims 12 and 24 will be rejoined and examined with the elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 9-21, 23-25 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of protecting a mouse from an organophosphate comprising administering to the mouse an expression cassette comprising a

promoter operably linked to a gene encoding PON1, wherein the expression of PON1 results in detoxication of the organophosphate, does not reasonably provide enablement for treating or protecting a cell or a subject from an organophosphate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Applicants claim a method of treating a subject from an organophosphate toxin comprising administering an expression cassette comprising a promoter operably linked to a gene encoding PON1. More specifically, the applicants claim either treating or protecting Gulf War Syndrome in a subject or protecting a subject from a chemical warfare agent. Claims 1 and 3-5 and 9-20 can read on a method for in a cell either in vivo or in vitro. The claims are considered broad. With regard to the claimed method practice in vitro, applicant's disclosure does not teach the skilled artisan how to use this method in vitro. The only in vitro embodiment involves testing recombinant adenovirus in 293 cells (page 41). The only disclosed use for transferring and expressing PON1 is for treatment (protecting or treating) of an in vivo cell from a toxin. In view of the guidance in the specification, the claimed methods are directed to a method of gene therapy.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.* 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is

a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In Re Wands* as set forth above.

At the time the application was filed, gene therapy was considered to be unpredictable due to significant problems in several areas. The state of the art, exemplified by Anderson et al., Nature, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Thus, at the time the application was filed, the state of the art for gene therapy was considered highly unpredictable.

For additional reviews of the unpredictability of the gene therapy art, see Davis (Curr. Opin. Biotechnol., 2002 3:128-31); Schmidt-Wolf et al. (TRENDS in Molecular Medicine 9:67-72, 2003) and Stribley et al. (Fertility and Sterility 77:645-57, 2002). Schmidt-Wolf teaches the problems of using viral vectors in gene therapy (page 67). Stribley teaches that current vectors lack specific targeting in vivo, inefficient long-term expression, and low transfection rates (page 649) and the problems of using adenoviral vectors in gene therapy (page 650).

The instant specification teaches that paraoxonases can hydrolyze organophosphates and protect against such toxicity (page 2). Paraoxonases can act on several organophosphate substrates (page 2). Paraoxonase activity is present in the serum of most mammals as well as in tissue such as the liver, kidney, small intestine (page 3).

Applicants teach the use of recombinant adenovirus comprising a gene encoding either PON1 type R or type Q followed by chlorphyrifos challenge in mice (pages 43-44). The serum paraoxonase activity was higher in the type R treated group compared to the control group. The

serum paraoxonase was not significantly different from that of the control group. The mice receiving the adenovirus were protected or partially protected from chlorphyrifos.

The invention involves one of the most complex areas of medicine/molecular biology, gene therapy for protecting from toxins in humans. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed expression cassettes generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices all nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In addition, with respect to treating a genus of subjects using the claimed method, the specification is not considered enabled. The breadth of the claim is considered broad because the claim reads on a genus of subject (including humans, primates, sharks, birds, cats, dogs, mouse, rats, monkeys, insects, farm animals, etc.). The claimed methods read on protecting a subject from exposure of an organophosphate toxin, wherein the subject could be exposed to the toxin, 1 second, 1 minute, 1 hour, 1 day, 1 year, 10 years, etc. The transient nature of gene therapy and the time required for each vector (viral or non-viral vector) to transfect cells and express the DNA varies is well known to the skilled artisan. The specification does not address these issues. As stated in the specification some subjects express PON1 and some subjects do not express PON1 at all (page 3). In view of the specification, it appears that the main goal of the claimed method is protecting humans exposed to chemical warfare agents. As stated above, the applicants teach expressing human PON1 in mice using an adenovirus comprising a CMV promoter. However, the art of record teaches that although the generating mouse lines that

express human PON1 using human cDNA constructs were not successful (Furlong et al., supra). Furlong futher teaches that, "Since the regulatory mechanism of human PON1 expression has not yet been identified, it is unknown whether any cis-acting elements required for PON1 transcription are included in these constructs (page 649)."

The art of record and the specification do not teach what amount of toxin is above the level that PON1 can hydrolyze. In view of the history of chemical warfare (WWI, WWII, etc.), the skilled artisan would understand that the goal of chemical warfare is to kill your opponent, which might result in the subject being exposed to a toxin (organophophate) that is above the level that PON1 can hydrolyze. The applicants assert that, at the time of the invention, studies with PON1 gene therapy have not been attempted (page 4). Thus, expressing PON1 in a genus of subjects for protecting the subjects against organophosphate toxins (chemical warfare agent) is considered unpredictable.

Furthemore, the specification does not teach the skilled artisan that it would be routine for the skilled artisan to reasonably extrapolate from protecting a murine model exposed to an organophosphate using the recited method to protecting a genus of subjects. The art of record teaches that the extrapolation is considered unpredictable. "Chemical warfare agent dose response curve can be quite steep leading the skilled artisan to question the concern over a very narrow range of sublethal dose levels" (page 8). "The extrapolation of findings from studies on the effects of chemical warfare agent exposure in animals and humans can be imprecise and unpredictable" (page 8). "The impacts of different methods of chemical warfare agent expsoure, such as topical, injection and inhalation, may result in varied manifestations and timings of effects even comparalbe concentratiosn and subject conditions" (page 8). "The preponderence of

information on the combined effects of low-level exposure is lacking" (page 8). See United Stated General Accounting Office: Report to Congressional Requesters, Chemical Weapons DOD Does not have a Strategy to Address Low-Level Exposures September 1998, pages 1-39.

In conclusion, the instant specification and claims coupled with the art of record, at the time the invention was made, only provide sufficient guidance and/or evidence to reasonably enable a method of protecting a mouse from an organophosphate comprising administering to the mouse an expression cassette comprising a promoter operably linked to a gene encoding PON1, wherein the expression of PON1 results in detoxication of the organophosphate and not for the full scope of the claimed invention. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any expression cassette cited in the claims, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicant's arguments filed 2/23/06 have been fully considered but they are not persuasive.

In response to applicant's argument that Anderson and Verma are irrelevant to the issue of enablement for gene therapy for an application claiming benefit of a filing date in 2001 because the articles are outdated, the argument is not found persuasive because the arguments of counsel cannot take the place of evidence in the record. See In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). The problems with gene therapy outlined by Anderson and Verma are still problems that

the skilled artisan encounters at the time the application was filed and currently. See Van Linthout et al. Current Pharmaceutical Design 2005, 11:2927-2940; Thomas et al. Nature, 4:346-358, 2003; and Juengst, BMJ, 2003, 326:1410-11. Thus, the issues of enablement set forth by Anderson and Verma are not irrelevant because, at the time the application was filed and currently, the problems of gene therapy still existed.

In response to applicant's argument that the remaining references are not discussed in the office action and these references actually support the enablement of gene therapy, the argument is not found persuasive because the references were cited to further support the unpredictability of gene therapy, at the time of filing. Some sections of Schmidt-Wolf et al. and Stribley indicate as pointed out by applicants that concerns of gene therapy are being addressed. However, applicant excludes other parts of the reference that teaches that problems still exist with gene therapy that have not been addressed at the time of filing. See page 649 of Stribley. While, it is acknowledged that other types of gene therapies have been cited in the art as treating a particular disease or genetic disorder using distinct material and methods, the art of record teaches that one skilled in the art can not reasonably extrapolate from one type of gene therapy to another type of gene therapy without an undue amount of experimentation and the art of record teaches that there is no universal protocol that can be reasonably extrapolated from one type of gene therapy to the claimed gene therapy method (See Van Linthout et al. (supra); Thomas et al.(supra); Juengst (supra); and Rosenberg, Science, 287, 1751, 2000).

In response to applicant's argument that the PTO has issued dozens of gene therapy patents, the argument is not found persuasive because every case is decided on its own merits. (*See In re Giolito*, 530 F.2d 397, 400, 188 USPQ 645, 648 (CCPA 1976). While, it is

acknowledged that other types of gene therapies have been cited in the art as treating a particular disease or genetic disorder using distinct material and methods, the art of record teaches that one skilled in the art can not reasonably extrapolate from one type of gene therapy to another type of gene therapy without an undue amount of experimentation and the art of record teaches that there is no universal protocol that can be reasonably extrapolated from one type of gene therapy to the claimed gene therapy method (See Van Linthout et al. (supra); Thomas et al.(supra); Juengst (supra); and Rosenberg (supra)).

In response to applicant's argument that it is not incumbent upon applicants to establish that in each and every scenario complete protection be provided, the argument is not found persuasive because the claimed method embraces (partial/full protection) of a cell or subject to short-term or long-term exposure to an organophosphate toxin. In addition, the claimed method embraces future protection of a cell or subject from an organophosphate toxin.

MPEP 2164.08 recites:

> All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. See, e.g., AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003).

The art of record and the specification do not teach what amount of toxin is above the level that PON1 can hydrolyze. The applicants assert that, at the time of the invention, studies with PON1 gene therapy have not been attempted (page 4). "If little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as

to how to make and use the invention in order to be enabling." See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). In view of the art of record, expressing PON1 in a genus of subjects for protecting the subjects against organophosphate toxins (chemical warfare agent) is considered unpredictable. Furthemore, the specification does not teach the skilled artisan that it would be routine for the skilled artisan to reasonably extrapolate from protecting a murine model exposed to an organophosphate using the recited method to protecting a genus of subjects. The art of record teaches that the extrapolation is considered unpredictable. See United Stated General Accounting Office: Report to Congressional Requesters, Chemical Weapons DOD Does not have a Strategy to Address Low-Level Exposures September 1998, page 8 and Thomas (supra). In view of the prior art, it appears that there is a variation between species of subjects because individual subject responds differently to toxins. The specification and the prior art do not teach how each individual subject responds to organophosphate toxins and depending on several parameters (e.g., individual, amount ot toxin, weight, route of exposure, metabolism, level of endogenous PON1 expression, etc.), whether there would be destruction of tissue by organophoshphates in the blood before the gene therapy method was administered.

In response to applicant's argument that the skilled artisan could reasonably extrapolate (correlate) from the murine model used in the specification to practicing the methods in a genus of subjects, the argument is not found persuasive because neither the specification nor the prior art teach that the mouse model is recognized as correlating to protecting either a genus of cells or a genus of subjects from an organophosphate toxin. "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the

art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). As stated by applicants, the study of PON1 gene therapy has not been attempted (page 4). The art of record teaches that correlating results from an animal model to a genus of animals is considered unpredictable. See United Stated General Accounting Office: Report to Congressional Requesters, Chemical Weapons DOD Does not have a Strategy to Address Low-Level Exposures September 1998, page 8 and Thomas (supra).

Thus, the enablement rejection remains for the reason(s) of record.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, SPE – Art Unit 1635, can be reached at (571) 272-4517.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
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BRIAN WHITEMAN
PATENT EXAMINER